REMARKS

With reference to the substituting group R^3, the broad compound and composition claims originally claimed two species, i.e., a first species wherein R^3 is an alkyl group having 1 to 5 carbon atoms and a second species wherein R^3 is an alkoxy group having 1 to 5 carbon atoms. The claims have been amended so that they are now directed only to the species wherein R^3 is an alkoxy group containing 1 to 5 carbon atoms. It is noted that the four compounds set forth in original Claim 5 (the only four specific compounds named in the claims) are all compounds in which R^3 is an alkoxy group. Page 9 of the specification, lines 15-21 discloses in detail the various R^3 alkoxy groups and notes that R^3 is most preferably an alkoxy group when R^2 is a methyl group. This is the subject of original Claim 4. Page 9, line 17, specifically discloses R^3 as an isopropoxy group. The disclosure on page 9 supplemented by the disclosure throughout the specification which discloses compounds wherein R^3 is an isopropoxy group is relied upon to support Claims 19, 20, 26 and 27 which are specific to compounds wherein R^3 is the isopropoxy group. It is respectfully submitted that the applicable law holds that such disclosure supports these claims, see In re Driscoll, 195 USPQ 434 (CCPA 1977); In re Johnson et al, 194 USPQ 187 (CCPA 1977); and In re Wertheim et al, 191 USPQ 90 (CCPA 1976).

Claim 5 has been replaced by Claims 28-31. Claim 32 names compound No. 19 disclosed on page 12 of the specification. Claims 21-25 are a parallel set of claims directed to the pharmaceutical compositions

Applicants' claims are rejected under 35 USC 103 as being unpatentable over the Durckheimer USP 4,278,793. Before discussing the rejection, applicants' invention is restated to place it in the context of the art.

Cephalosporin compounds have been widely acknowledged for their potent activity. Certain of these compounds have exhibited highly effective antibacterial activity which is broad spectrum against gram-positive and gram-negative bacteria. Unfortunately, the prior art compounds which exhibit this combination of highly effective activity and broad spectrum activity against both gram-positive and gram-negative bacteria did not have the desired effectiveness when administered via oral administration. Since about 50% of the Staph infections (caused by gram-negative bacteria) are outpatient infections (the statistics being for Japan), the lack of a highly potent broad spectrum compound which is effective via oral administration was an acknowledged problem in the field.

Applicants' invention solved this problem and provides the desired compounds and pharmaceutical compositions containing such compounds. Applicants' claimed compounds have been established to be potent antibacterial materials having broad spectrum activity against both gram-positive and gram-negative bacteria and to exhibit this effectiveness when administered via oral administration.

Applicants' claims and compositions are rejected under 35 USC 103 as being unpatentable over the Durckheimer USP 4,278,793 on the ground that applicants'

> "Compounds as claimed appear within generic disclosure of reference with methoxymethyl substituent suggested at Col. 7, line 63."

The generic disclosure of the general formula in the reference contains six variables, i.e., R_1, R_2, R_3, R_4, X and A. In order to arrive at applicants' claimed compounds from the disclosure of the reference, it is necessary to pick from tens of thousands and possibly hundreds of thousands of combinations and permutations, the selection of the five variables resulting in applicants' claimed compunds.

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The methoxymethyl group referred to in the Office Action which is "suggested" in Col. 7, line 63 is disclosed in the following context: It is included in the definition of "A" which is one of the five variables. Column 7,lines 17-27 disclose that "A" can broadly be about ten or eleven different types of groups and "preferably chlorine or bromine, or $-CH_2Y$". This is followed by the definition of possible Y substituents starting at Col. 7, line 27 through Col. 22, line 31 which apparently discloses thousands or tens of thousands of possible Y substituents. There is no disclosure in this reference which would lead one skilled in the art to select the methoxymethyl group as the "A" substituent.

The reference discloses about 530 specific compounds in Columns 33-139 (53 pages averaging about 10 compounds per page). An analysis and survey of these cmopounds would lead to the understanding that when the "A" group is $-CH_2Y$, the Y group is preferably one of the substituted heterocyclic groups (such as thiazolyl, thiadiazolyl, triazolyl, oxadiazolyl and tetrazolyl) or an acetoxy, acetylthio or carbamoyl group because no other "nucleophilic" group such as methoxy are specifically disclosed.

It is respectfully submitted that not only are there no teachings in the reference which would lead one skilled in the art to select the methoxymethyl group as the "A" substituent, the reference disclosure counterindicates selection of the methoxymethyl group because of the disclosure of many specific compounds having groups other than the methoxymethyl group at the No. 3 position thereby indicating that such other groups are preferred.

It is evident from the disclosure of the reference, that the gist of the reference invention resides in the substitution at the 7-position. The other groups such as the group "A" are those often very broadly disclosed in prior art references relating to the cephalosporin prior art. There is nothing in the voluminous cephalosporin prior art which would lead one to select from the voluminous disclosure of this reference (Col. 7 - Col. 22) the methoxymethyl group as the substituent at the No. 3 position and then to select from all of the many other possibilities, the substituents specified at the No. 4 and No. 7 positions to arrive at applicants' claimed compounds.

The patentability of applicants' claimed compounds and compositions relative to the issue of obviousness in view of the Durckheimer disclosure is a variant of the situation commented upon by Mr. Alton D. Rollins in the May 1982 Journal of the Patent Office Society, pages 291-294. It is respectfully submitted that it is clear from Mr. Rollins discussion and the cases discussed and/or cited therein that applicants' claims, directed to a narrow subgenus which is an unobvious selection from the shotgun disclosure of the reference, are patentably distinguished from the reference.

Enclosed herewith is a DECLARATION PURSUANT TO 37 CFR 1.132 of Dr. Nagao dated December 20, 1982 which discusses the fact that the prior art was in need of antibiotics having (1) a wide range (broad) activity against bacteria generally; (2) high activity against gram-positive bacteria; and (3) exhibiting the aforenoted activity when administered via oral administration. The Declaration also contains comparative data which establishes that applicants' claimed compounds can be administered via oral administration and are effective antibacterial agents when administered in this manner whereas the Durckheimer compounds are not.

The compounds on page 9 of Dr. Nakao's Declaration in which Z is the acetoxymethyl group, the 1-methyl-1H-tetrazol-5-ylthiomethyl group or 2-mehtyl-1,3,4-thiadiazol-5-ylthiomethyl group are compounds of the cited Durckheimer patent. The data establishes that the recovery rate in urine of Durckheimer's compounds in their carboxylic acid form (i.e. Y is hydrogen) are not improved by esterifying them to the extent that such esters can be orally administered and exhibit useful activity. The data also establishes that applicants' claimed compounds wherein Z is methoxymethyl and wherein the compound is esterified so that it falls within the scope of applicants' claims, have a high recovery rate in urine and, therefore, are useful when administered via oral administration.

It is respectfully submitted that applicants have established that their claims are directed to subject matter which is patentably distinguished from the cited Durckheimer reference.

Page 4, lines 19 and 20 of applicants' specification have been amended to identify European Patent Application 29,557 (hereinafter referred to as "EP 29,557" and/or "Fujisawa"), which was published June 3, 1981. Fujisawa discloses a class of compounds in which the subsituents at the No. 3 and the No. 7 positions are identical with those of applicants' claimed compounds. Example 16 of the Fujisawa application discloses 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid, which is the free acid form of certain of applicants' claimed compounds.

The Fujisawa specification discloses that the Fujisawa group R^3 (which is a different R than in applicants' claims) at the 4-position may be either carboxy or a "protected" carboxy group. On pages 21-22 Fujisawa discloses that "Suitable 'protected carboxy group' may include an esterified carboxy group which is conventionally used in penicillin or cephalosporin compounds at their 3rd and 4th position thereof." and subsequently enumerates groups such

as lower alkyl esters, lower alkanoyloxy(lower)alkyl esters, benzhydryl esters and the like.

Fujisawa on pages 51-52 discloses antibacterial activity of several Fujisawa compounds which are all carboxylic acids. Fujisawa does not disclose any compounds having a "protected carboxy group" as having been actually tested for antibacterial activity.

Fujisawa discloses 43 Examples which must be construed to be preferred embodiments. Of these, Examples 4-11, 15-24, 26, 27, 29, 31-37, 43 and 44 relate to carboxylic acids, Examples 1, 2, 12, 25, 28, 30 and 38-42 relate to benzhydryl esters, and Examples 3, 13, 14 relate to t-butyl esters. The Examples are limited to carboxylic acids, and their benzhydryl esters or t-butyl esters.

Applicants' specification, page 5, and Dr. Nakao's Declaration, page 9, establish that the Fujisawa compound (at least the compound of Example 16 in Fujisawa EP 29,557) in its carboxylic acid form exhibits a poor recovery rate in urine and is, therefore, unsuitable for oral administration. The same paragraph on page 5 of applicants' specification points that the t-butyl and benzhydryl esters of cephalosporin compounds are well known to be chemically stable and are not believed to be readily convertible in vivo to the corresponding carboxylic acid, and, as a result, are not effective in actual use.

A consideration of the foregoing leads to the conclusion that "protected carboxy group" as used in Fujisawa refers to protecting groups commonly used for the chemical protection of the carboxy group so that it will not be hydrolyzed in vivo to liberate the corresponding biologically active carboxylic acid group. It, therefore, follows based on applicants' tests

including those reported in Dr. Nakao's Declaration that the Fujisawa compounds (at least those having substituents at the No. 3 and No. 7 positions which are identical with applicants) should not be expected to be suitable for oral administration despite the broad statement in the paragraph bridging pages 1 and 2 of the Fujisawa published application that the compounds disclosed therein are "...useful as antimicrobial agents, especially oral administration." As noted, Fujisawa compounds have the same substituting groups at the No. 3 and 7 positions as applicants' compounds. Applicants' data establish that the free acid and the Fujisawa exemplified protecting groups are not useful for oral administration.

It is respectfully submitted that the foregoing establishes that applicants' claimed compounds and compositions which are useful for oral administration are directed to a different invention than the invention disclosed by Fujisawa and that applicants' claimed invention is not obvious in view of the Fujisawa disclosure.

Applicants also wish to make of record that the subject matter claimed in the present application is supported by the disclosure in applicants' earliest priority Japanese Application, i.e. No. 136449/1980 filed September 30, 1980, which predates the earliest Fujisawa publication date of June 3, 1981. A sworn translation (in the form of a Declaration) will be filed shortly.

The Fujisawa European Patent Application and the corresponding Japanese published Patent Application are discussed on pages 4 and 5 of applicants' specification because they were published when applicants' United States application was in preparation and a discussion thereof is included to further establish the background of the invention although these publications are subsequent to applicants' earliest priority date.

Applicants are also aware of another material reference published prior to the present application, namely, the Roussel-Uclaf European Patent Application 34,536 (referred to hereinafter as "EP 34,536") which was published August 26, 1981. EP 34,536 broadly discloses the compounds which are claimed in the present application. Applicants rely upon their aforeidentified earliest priority application, namely Japanese Patent Application No. 136449/1980 filed September 30, 1980, as the date of invention for which the present application is entitled under 35 USC 119. As such, applicants' date of invention is earlier than the publication date of EP 34,536.

The four specific compounds which were the subject of original Claim 5 and which are now the subject of Claims 21-24 and 28-31 are specifically disclosed in applicants' priority Japanese Application No. 136449/1980. The compound which is the subject of Claims 25 and 32 is not specifically disclosed in Japanese Application No. 136449/1980. It is noted that EP 34,536 does not disclose the specific compound which is the subject of applicants' Claims 25 and 32. The applicable law is that when a priority application which predates a reference (1) discloses the invention which is disclosed in the intervening reference and further when the priority application (2) discloses the same invention claimed in the United States application, the priority document serves to provide a date of invention for subject matter claimed in the United States application, which date is prior to the publication date of the intervening reference. The applicable law is set forth in In re Stempel, 113USPQ 77, 81 (CCPA 1957) and In re Spiller, 182 USPQ 614, 619 (CCPA 1974). The CCPA subsequently referred to these cases as defining the applicable law at page 784 of the decision in In re Scheiber, 199 USPQ 782 (1978). See also In re Dardick, 181 UPSQ 834, 838 (CCPA 1974); In re Stryker, 168 USPQ 372 (CCPA 1971); In re Hostettler et al, 148 USPQ 514 (CCPA 1966); and In re Clarke, 148 USPQ 665, 671 (CCPA 1966).

It is respectfully submitted that applicants' claims are directed to subject matter which is patentably distinguished from the prior art. Reconsideration is requested. Allowance is solicited.

Copies of the publications identified in the enclosed form PTO-1449 which have been discussed in the present paper and/or applicants' specification are enclosed herewith.

A divisional application directed to the alkyl species which has been deleted from the claims by this amendment is being filed on the same day as this amendment.

Please apply the enclosed check in the amount of $120.00 as the fee for the additional claims.

Respectfully submitted,

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HG/fs

Encs::

Check $ 50.00 appl.
Check $120.00

DECLARATION PURSUANT TO 37.CFR 1.132 of Hideo Nakao dated December 20, 1982
Form PTO-1449 and references cited therein.

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